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Comparing efficacy and tolerability of ibuprofen and paracetamol in fever

John McIntyre, David Hull

Abstract

The purpose of this study was to compare antipyretic activity and evaluate tolerability of ibuprofen and paracetamol suspension in the treatment of febrile children. It was designed as a double blind, parallel group, multiple dose study comparing ibuprofen (20 mg/kg/24 hours) with paracetamol (50 mg/kg/24 hours) given at six hourly intervals for a maximum of 12 doses. Children on paediatric wards between the ages of 0·2 and 12 years, with fever as defined by an axillary temperature ≥37·5°C, were included. The main outcome measures were: change in axillary temperature; palatability of medication; changes in irritability and clinical condition; overall efficacy at the end of treatment; and number and nature of adverse events.

The mean temperature change from baseline at four hours was −1·8°C and −1·6°C in ibuprofen and paracetamol groups respectively. In both groups: median palatability score was 'no reaction'; median irritability score at end point was 'not irritable'; median score for change in clinical condition was 'improved'; and median score for overall efficacy was 'good effect'. The proportion of patients experiencing adverse events was similar in both groups, the majority of events having doubtful or no relationship to therapy and being mild in severity.

In conclusion, ibuprofen suspension was as effective and well tolerated as paracetamol in treatment of fever in young children.

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Antipyretic agents have an established place in managing febrile children. As fever is common in childhood illnesses, antipyretic drug use is widespread.[1] It is therefore important to be confident that the drugs given are safe and efficacious in children with a fever from a variety of causes.

In 1986 the Committee on Safety of Medicines advised doctors not to prescribe aspirin routinely for children under 12 years of age because of a possible association with Reye's syndrome.[2] This left paracetamol as the only readily available antipyretic. Although extensively used and with a good safety record there have been recent reports indicating the margin of safety of frequent therapeutic doses in infants and young children a lot lower than previously appreciated.[3]

Ibuprofen is recommended in treatment of juvenile arthritis and is well tolerated. It is also an effective antipyretic.[4] It is therefore a potential alternative to paracetamol. Previous studies have indicated an appropriate dose range for ibuprofen.[5] In many studies that have compared ibuprofen and paracetamol, young children and those with wheezing and asthma have been excluded. The objectives of this study were to compare the antipyretic activity and evaluate the tolerability of ibuprofen suspension and paracetamol suspension used in treating febrile children, including young infants and those with common paediatric illnesses.

Methods

STUDY DESIGN AND PATIENTS

This was a double blind, parallel group, multiple dose study and was given approval by the local ethics committee. Written informed consent was obtained from the parent or legal guardian and from the child when able to give consent. Those entering the study were inpatients at a single hospital, between two months and 12 years of age, of either sex, and with an axillary temperature of 37·5°C or above. Patients were excluded if their weight was below the third centile for age, they were receiving anticoagulant treatment, had a history of intolerance to ibuprofen, paracetamol or similar compounds, had previous occurrence or current symptoms of peptic ulceration or gastrointestinal bleeding, or had severe liver, heart, kidney, or systemic disease including malignancy. Medication that could interfere with the study was not permitted during nor in the six hours before entry to the study.

The following were recorded at entry to the study: age, sex, weight, primary diagnosis, treatment received during the previous month, and any history such as asthma, wheezing, or convulsions.

The study medication was prepared by Boots Pharmaceuticals, as orange flavoured saccharin free suspension. Randomisation was in blocks of four to allow for equal numbers in each treatment group. The dose of medication was determined by age and ibuprofen at approximately 20 mg/kg/24 hours or paracetamol at 50 mg/kg/24 hours was given in divided doses. Medication was administered orally six hourly if required, up to four doses in each 24 hour period, for a maximum of three days (12 doses).

Patients were withdrawn from the study if at any time continued participation could be considered detrimental to their well being.

Department of Child Health, University Hospital, Nottingham
J McIntyre
D Hull

Correspondence to:
Dr J McIntyre, Jenny Lind Children's Department, Norfolk and Norwich Health Care NHS Trust, Brunswick Road, Norwich, Norfolk NR1 3SR.

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EVALUATIONS

At the first dose, axillary temperature was recorded and then at hourly intervals for six hours and thereafter every six hours or immediately before any subsequent doses. After the first dose, palatability was recorded by observation of the child's reaction or by request if the child was aged over 7 years, using a five point scale (from 0=disliked the taste a lot to 4=liked the taste a lot). Irritability was assessed using a three point scale (from 0=very irritable to 2=not irritable). Before subsequent doses the change in clinical condition was noted on a five point scale (from 0=much worse to 4=much improved), and after, irritability was reassessed and other measures of cooling noted. When the last dose of study medication was given, or when the fever had resolved, overall efficacy of the medication was recorded on a four point scale (from 0=no effect to 3=very good effect). Occurrence of any adverse events were documented with respect to nature, causality, and severity.

STATISTICS

The planned sample size was 75 patients in each treatment group: with 90% power and a 5% significance level, assuming a variability of 1·07°C the detectable difference for the change from baseline in temperature over a four hour period was 0·56°C. The variability observed during the trial was 1·18°C. All statistical tests performed were two tailed with significance determined by reference to the 5% level. The null hypothesis was always that ibuprofen and paracetamol were equivalent. Change in body temperature at four hours was compared between treatment groups using an analysis of covariance with a factor for treatment and age as a covariate. Ordinal measures of palatability, change in irritability from baseline to end point, change in clinical condition at end point, and overall efficacy were compared between treatment groups using the Wilcoxon rank sum statistic. Withdrawals and the time for the temperature to fall below 37·5°C were compared using the log rank test. The number of patients experiencing adverse events and the number of patients whose temperature fell by 1°C or more at four hours were each compared using the χ^2 test.

Results

All 150 patients who entered the study provided at least one valid post-baseline efficacy assessment and all available efficacy data were included in the analysis on the basis of intent to treat. A summary of presenting problems at admission is shown in table 1.

DEMOGRAPHICS AND BASELINE FEATURES

The treatment groups were comparable in age, sex, and weight. In the ibuprofen group (42 boys and 34 girls) the median age was 1·8 years (range 0·4–11·6 years), the median weight 11·9 kg (range 6·7–45 kg), and 20 were ≤12 months of age. In the paracetamol group (47 boys and 27 girls) the median age was 1·6 years (range 0·2–9·4 years), the median weight 11·9 kg (range 5·8–34 kg), and 20 were ≤12 months of age. At entry, in the ibuprofen group there were 11 patients with a primary diagnosis of wheezing and 21 with a past history of wheezing and/or asthma; for the paracetamol group there were four and 12 patients respectively. All 150 patients entered into the study took at least one dose of study medication, although one patient did not ingest her medication. Thirty five patients in the ibuprofen group and 28 in the paracetamol group were receiving concomitant treatment at entry.

Table 1 Summary of primary diagnosis at admission (n=150)

Primary diagnosis	*Total No of patients*
Febrile convulsion	35
Viral illness (non-specific)	29
Chest infection	25
Asthma/wheezing	15
Croup	10
Gastroenteritis	8
Bronchiolitis	8
Soft tissue infection	6
Urinary tract infection	4
Otitis media	3
Tonsillitis	3
Herpes stomatitis	1
Septic arthritis	1
Tracheitis	1
Septicaemia	1

EFFICACY DATA

The main results are summarised in table 2. The difference between treatments for the mean change from baseline in body temperature at four hours was −0·2°C (95% confidence interval −0·6 to 0·2; p=0·39). The largest mean decreases in body temperature occurred during the first five hours. In the ibuprofen group the maximum mean decrease from baseline was 2°C at three hours and in the paracetamol group 1·7°C at two, three, and four hours. The changes in actual mean temperature are shown in the figure. After 36 hours there was only a small proportion of patients remaining in the study so the mean decreases beyond this have not been plotted.

During the study, the temperature fell below 37·5° for 73/76 (96%) patients in the ibuprofen group and 66/74 (89%) patients in the paracetamol group. There were no statistically significant differences between the treatment groups in: (a) the distribution of the times until the temperature fell below 37·5°C (median times of 2 hours and 1·4 hours for ibuprofen and paracetamol groups respectively; p=0·25) and (b) the distribution of the times until the second dose (median times of six hours in both treatment groups; p=0·44). Only 14 children in the ibuprofen group and 13 in the paracetamol group received more than four doses of medication the majority having withdrawn due to recovery.

MEASURES OF PALATABILITY, IRRITABILITY, CHANGE IN CLINICAL CONDITION, AND OVERALL EFFICACY

The results summarised in table 2 show no significant difference between the groups apart

Table 2 Summary of main results

	Ibuprofen	*Paracetamol*	*p Value*
Mean change from baseline in body temperature at 4 hours	−1·8°C	−1·6°C	0·39
No (%) with reduction ≥1°C at 4 hours	52/69 (75)	48/66 (73)	0·73
Median palatability score	2 (no reaction)	2	0·43
No (%) of patients with improved irritability score	9/50 (18)	21/56 (38)	0·047*
Median score for change in clinical condition	3 (improved)	3	0·08
Median score for overall efficacy	2 (good effect)	2	0·16

*See text.

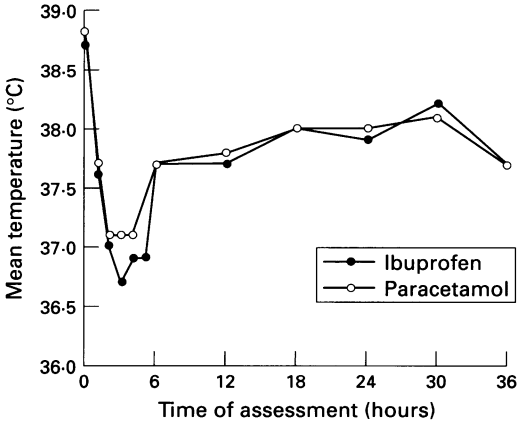
from the change in irritability. Although the median change from baseline in irritability was 0 in both groups a larger proportion of paracetamol patients had an improved irritability score; 21/56 (38%) paracetamol patients improved compared with 9/50 (18%) ibuprofen patients (p=0·047). However, the median irritability scores at baseline for ibuprofen and paracetamol treated patients were 2 (not irritable) and 1 (slightly irritable) respectively. Within this parameter it is likely that the difference favouring paracetamol treated patients reflects the greater potential for improvement among those randomised to paracetamol.

Of other methods of cooling, stripping of clothing was the most frequently employed additional measure in both treatment groups, being used on at least one occasion in 42/70 (60%) ibuprofen treated patients and in 55/70 (79%) paracetamol treated patients.

SAFETY RESULTS

Sixty six out of 76 (87%) patients in the ibuprofen group and 64/74 (87%) patients in the paracetamol group withdrew due to recovery. Seven patients in the ibuprofen group and eight in the paracetamol group withdrew due to adverse events and/or lack of efficacy. The adverse events associated with withdrawal for the four patients receiving ibuprofen were: urticarial rash, vomiting, abdominal pain and sore throat, and one patient admitted with an 'irritable hip' required surgery. In the paracetamol group three patients withdrew due to a nose bleed, purpuric spots at the site of the blood pressure cuff, and meningococcal meningitis. Three patients in the ibuprofen group and two patients in the paracetamol group withdrew for other reasons.

Twenty four out of 150 patients (16%) experienced 34 adverse events during the study: 10/76 patients (13%) in the ibuprofen group had 16 events and 14/74 patients (19%) in the paracetamol group had 18 events. The number experiencing adverse events was not significantly different between the treatment groups (p=0·34). The majority of adverse events had a doubtful or no relationship to treatment and most were considered mild. In 14 of the adverse events reported there was considered to be no relationship to treatment. For the remaining 20 reports the results are summarised in table 3.



Change in temperature over time.

No patients were reported to have experienced an asthma attack during the study but two, both in the paracetamol group, experienced mild wheezing. One had no history of wheezing and was entered into the study with a chest infection; the other had a history of wheezing.

Discussion

Although some have argued that a fever may be beneficial,[6] it is generally accepted that antipyresis does not seem to prolong the illness or adversely affect the outcome.[7] While appropriate management of the illness must be the central part of looking after febrile children, concern for the comfort of children has made antipyretic use commonplace. Antipyretic medication must therefore be both safe and effective. Confidence in paracetamol, the most commonly used antipyretic in children, results from its long standing use. Aspirin had a similarly long standing use but was withdrawn as an antipyretic after reports of a possible association with Reye's syndrome in the USA.[2]

In 1990, ibuprofen became available for use in children as an antipyretic. It is a non-steroidal anti-inflammatory agent and thus may have adverse effects on gastrointestinal and renal systems[8] and be unhelpful in asthmatic patients.[9] Previous studies have established a good safety profile for ibuprofen in children through its use in juvenile arthritis.[10 11] Its antipyretic properties have also been established.[12–15] However, these antipyretic studies tested a single dose and excluded children under 2 years old. Multiple dose studies have also excluded children less than 2 years old,[15 16] and many studies exclude children of all ages with wheezing or asthma. However, many children who would be given an antipyretic are under 2 years old and present with a fever due to a respiratory tract infection that can also cause wheezing.

In this study, we attempted to evaluate both efficacy and tolerability of paracetamol and ibuprofen when used in a way likely to reflect common practice. Patients receiving ibuprofen were of a wide age range (0·4 to 11·6 years); 26% of patients were aged 12 months or less; they had a broad number of illnesses typical of paediatric practice, 14% having a primary diagnosis of wheeze/asthma and 28% with a history of wheezing or asthma.

In this context paracetamol and ibuprofen were shown equally effective antipyretics. They were regarded as equally palatable and

Table 3 Adverse events after excluding those not related to treatment

	Ibuprofen			*Paracetamol*		
Adverse event	*No of reports*	*Severity*	*Relationship to treatment*	*No of reports*	*Severity*	*Relationship to treatment*
Maculopapular rash	3	Mild	Doubtful			
	1	Mild	Possible			
Urticaria	1	Mild	Possible			
Respiratory distress				1	Mild	Doubtful
Sore throat	1	Mild	Doubtful			
Epistaxis				1	Mild	Doubtful
Cough				1	Mild	Doubtful
Asthma				2	Mild	Doubtful
'Hyperactive'	1	Mild	Doubtful			
Convulsion				1	Mild	Doubtful
Vomiting	2	Mild	Doubtful	2	Mild	Doubtful
Diarrhoea	1	Mild	Possible			
Abdominal pain	1	Mild	Doubtful			
Other				1	Mild	Doubtful

although a larger proportion of patients in the paracetamol group had an improved irritability score, it is likely that the difference favouring this group reflects the greater potential for improvement among those patients randomised to paracetamol. At the study end point there were no statistically significant differences for change in clinical condition, the median score being 3 (improved) in both groups, and overall efficacy, the median score being 2 (good effect) in both groups. There were no statistically significant differences between the groups in the numbers of patients with adverse events. Ten patients out of 76 (13%) in the ibuprofen group had 16 adverse events and 14/74 (19%) patients in the paracetamol group had 18 adverse events. These were mostly mild, with the majority considered to have a doubtful or no relationship to study treatment. No treatment related adverse events were recorded in the respiratory system for patients in the ibuprofen treatment group. Because of previous concern about the use of non-steroidal anti-inflammatory drugs in asthma,[9] further evaluation of ibuprofen in the wheezy/asthmatic child would be necessary.

In conclusion, ibuprofen and paracetamol in the doses used were shown to be equally effective and well tolerated in the treatment of fever in young children. Although the treatments appeared equally safe, it will require continuing vigilance from those caring for children before ibuprofen is given the confidence afforded paracetamol.

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